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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

WANG, SHENGJUN

ART UNIT

PAPER NUMBER

1617

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/529,053

Applicant(s)

WILLIAMS ET AL.

Examiner

Shengjun Wang

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2006.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-44 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 26-44 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 1, 2006 has been entered.

Claim Rejections 35 U.S.C. 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 26, 27, 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Weithmann et al.

3. Reading the claims in light of the specification, the claims are construed as require administration of leflunomide, its active metabolite, related derivatives, or anti-viral active metabolites thereof, to a human in an amount effective to inhibit viral virion assembly, such amounts can vary from 0.1 mg/day to 80 mg/day. (see pages 13-19). Note the human herein may be either infected, or not infected with the viruses. The claims read on both treatment or prophylactic treatment of viral infection (see the discussion in Board's decision, pages 4-5 in particular).

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1. Weithmann et al. teach a method of treating disorder in which interleukin 1 beta is involved. The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. See, particularly, the abstract and the claim. The dosage may range from 3-50 mg daily, but may be higher if required. See, particularly, column 3, lines 7-16. Note, treating HIV patient would have inherently provided a prophylactic treatment against herpes viral infection, other any other viral infection. As to the limitation "to inhibit viral virion assembly," The instant claims are directed to effecting a biochemical pathway with an old and well known compounds. The argument that such claims are not directed to the old and well known ultimate utility (treating viral infection) for the compounds, e.g., leflunomide, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates.

Claim Rejections 35 U.S.C. 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 26, 27, 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870), in view of Flamand et al.

3. Weithmann et al. teach a method of treating disorder in which interleukin 1 beta is involved. The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. See, particularly, the abstract and the claim. The dosage may range from 3-50 mg daily, but may be higher if required. See, particularly, column 3, lines 7-16.

Weithmann et al. does not teach expressly the amount effective to inhibit viral virion assembly, Weithmann et al. also do not teach expressly the method for treating herpes.

4. However, Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. See, particularly, the abstract.

5. Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Weithmann for treating herpes infections.

6. A person of ordinary skill in the art would have been motivated to employ the method of Weithmann for treating herpes infections, because herpes infection is known to be involved interleukin 1 beta. Further, the optimization of a result effective parameter, e.g., effective amount for a therapeutical dosage of a known therapeutical agent, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. It is noted the effective amounts disclosed by Weithmann et al. are well within the effective amounts herein (from 0.1 mg/day to 80 mg/day, see pages 13-19). Further, treating a disease with an agent in a host would lead the agent contacting the pathogenic cell. A method known to be useful for treating

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viral infection would have been reasonably expected to be useful for prophylactic purpose. Finally, since leflunomide is effective against virus through different mechanism, it would have been reasonably expected to effective against those virus with resistance to antiviral agent that inhibit viral DNA replication. As to the limitation “for inhibiting viral replication in cells,” note the functional limitation of the method is not seen to make the otherwise obvious method patentable distinct. The instant claims are directed to affecting a biochemical pathway with an old and well known compounds. The argument that such claims are not directed to the old and well known ultimate utility (treating viral infection) for the compounds, e.g., leflunomide, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant’s attention is directed to *In re Swinehart*, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated “is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art.” In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

7. Claims 34 and 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

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Weithmann et al. do not teach expressly the employment of addition antiviral agent in the method.

8. However, Hammer teaches that several pyrimidine compounds, including uridine compounds, are known antiviral agents. See, particularly, page s3.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds with other antiviral agents such as those known pyrimidine compounds. Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

Claims 26-33, 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095), in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722).

9. Coghlan et al. teaches compounds with general structures that encompass leflunomide or its active metabolite, and meet the limitation of general formula as defined in claims 38 and 44, the compounds have similar biological activity of leflunomide or its metabolite. See, particularly, the abstract, page 2, the examples and the claims. The expressly taught compounds includes

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those meet the leflunomide products (page 18-19 in the specification). Homologue of leflunomide (e.g., 5-methyl-isoxazole-4-carboxylic acid 2,2,2,trifluoroethylamide) have been expressly disclosed (page 10, line 35). These compounds are known to be useful for treating or preventing infectious disease caused by pathogenic microorganism, such as hepatitis and cytomegalovirus infection, particularly, HCMV. See, page 3, lines 7-30, page 4, lines 23-32. Note, amide of malononitrile recited in claims 37 and 43 are keto tautomer of the leflunomide metabolisms as defined in claims 38 and 44, such as A771726, and would have been expected to be the same as those enol tautomers.

10. Coghlan et al. does not teach expressly the employment leflunomide or its metabolite, or the particular amount herein for treating viral infections.

11. However, McChesney et al. teaches that both leflunomide and A771726 are known to be effective in preventing viral infection. See, particularly, the abstract at page 1717, and the materials and method at page 1717-1718.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis and CMV, and the others defined herein.

A person of ordinary skill in the art would have been motivated to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis, CMV or other viral infections herein defined, because these compounds are known to be useful for treating or preventing infectious caused by pathogenic microorganisms, and viral infection in particular. Further, both leflunomide and

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A771726 are known to be similarly useful as the other compounds. Furthermore, the reference teaches certain compounds that are structural homologs of the instantly claimed leflunomide, i.e., they differ only by a CH₂ group. The instant compounds are structural homologs of the reference compounds when they differ only by a CH₂ group. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compound because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results. In re Hass, 60 USPQ 544 (CCPA 1944); In re Henze, 85 USPQ 261 (CCPA 1950). Finally, since leflunomide is effective against virus through different mechanism, it would have been reasonably expected to effective against those virus with resistance to antiviral agent that inhibit viral DNA replication. As to the limitation "for inhibiting viral replication in cells," note the functional limitation of the method is not seen to make the otherwise obvious method patentable distinct. The instant claims are directed to effecting a biochemical pathway with an old and well known compounds. The argument that such claims are not directed to the old and well known ultimate utility (treating viral infection) for the compounds, e.g., leflunomide, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical

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intermediates. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

Claim 34-42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095), in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722), and further in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

Coghlan et al. (WO 94/24095) and Hammer as whole do not teach expressly the employment of pyrimidine compound in the method.

12. However, Hammer teaches that several pyrimidin compounds, including uridine compounds, are known antiviral agents. See, particularly, page s3.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds with other antiviral agents such as those known pyrimidine compounds. Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

Response to the Arguments

Applicants' amendments and remarks submitted February 27, 2006 have been fully considered, but are not persuasive.

As to the rejections under 35 U.S.C. 102, applicants' attention is directed to Board's claim construction.

"Reading the claims in light of the specification, therefore, we construe claim 16 to require administration of leflunomide, its active metabolite, related derivatives, or anti-virally active metabolites thereof, in an amount that is effective to inhibit viral growth or viral assembly', such amounts can vary from 0.1 mg/day to 80 mg/day for a human.

We do not interpret claim 16 to require administering leflunomide to a patient', i.e., in vivo administration. Claim 16 requires only contacting a cell that is susceptible to viral infection with a leflunomide product. It does not require administering a leflunomide product to a patient or a human or an animal. During examination, claims are given their broadest reasonable interpretation. See *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Since claim 16 is not expressly limited to an in vivo method, the broadest reasonable interpretation of the claim is that it also reads on in vitro methods.

We also do not interpret claim 16 to be limited to a method of treating cells that are already infected by viruses. Claim 25 (claim 29 as currently pending) adds to claim 16 the limitation that the "cells are virally infected." Since a dependent claim must further limit the claim from which it depends, see 35 U.S.C. § 112, fourth paragraph, that limitation by implication is not present in claim 16.

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Finally, we conclude that the preamble of claim 16 "for inhibiting viral replication in cells susceptible to viral infection" - requires only that the cells contacted with a leflunomide product are susceptible to viral infection. It does not require that the contacting be done with the intent of inhibiting viral infection. Rather, the preamble phrase "for inhibiting viral replication" merely recites the purpose or intended use of the claimed method and therefore is not a positive limitation. See *Pitnev Bowes Inc. v. Hewlett Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999):

If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality to the claim, then the claim preamble should be construed as if in the balance of the claim. . . . If, however, the body of the claim fully and intrinsically sets forth the complete invention, including all of its limitations, and the preamble offers no distinct definition of any of the claimed invention's limitations, but rather merely states, for example, the purpose or intended use of the invention, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation.

See also *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376, 58 USPQ2d 1508, 1513 (Fed. Cir. 2001) (Preamble reciting "a method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" was "only a statement of purpose and intended result. The expression does not result in a manipulative difference in the steps of the claim.").

Thus, we construe claim 16 to be directed to a method comprising contacting cells susceptible to viral infection with, e.g., leflunomide or its active metabolite in an amount effective to inhibit virion assembly, either in vitro or in vivo. We construe claim 22 to be

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directed to the same method, where the cells are also contacted with another antiviral agent in addition to the leflunomide product. (see pages 3-6 of Board's decision).

Similarly claim 26 as pending are construed as being "directed to a method comprising contacting cells susceptible to viral infection with, e.g., leflunomide or its active metabolite in an amount effective to inhibit virion assembly, either in vitro or in vivo." The "inhibiting viral infection" recited herein does not constitute any limitation to the claims. It is suggest that the limitation of claim 29 be incorporated in claim 26 and recite "in need thereof" in claim 26.

13. As to the rejections under 35 U.S.C. 103, over Weithmann and Flamand et al. Applicants contend the claimed invention is not obvious because (1) one of ordinary skill in the art is not motivated to administer an immunosuppressant; such as leflunomide to treat infection because a non-suppressed immune system is desirable to combat infection, (2) Flamand et al. does not show that IL-1 beta levels are actually elevated or (even if elevated) deleterious in animals infected by herpesvirus, (3) the cited art provides no reasonable expectation of success that leflunomide would in fact have a beneficial effect on IL-1 beta levels in animals infected by herpesvirus, (4) neither reference teaches the unexpected effects on viral virion assembly demonstrated by Applicants, and (5) neither reference teaches one to administer an amount effective to inhibit viral growth. The arguments are untenable. Regarding reason (1), it is noted that Weithmann teach interleukin 1 beta mechanism, not the immunosuppressant. Further, it is noted that Coghlan et al. particularly teach that immunosuppressants are useful for treating viral infections; as to reasons (2) and (3), it is noted that Weithmann particularly teaches the usefulness of leflunomide for treating disorder in which interleukin 1 beta is involved. Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. It would have been prima

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facie obvious to a person of ordinary skill in the art, considering the cited references as a whole, at the time the claimed the invention was made, to employ the method of Weithmann for treating herpes infections. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As to the alleged unexpected benefits, it is noted that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). With respect to reason (5), it is noted that the effective amounts disclosed by the cited references are within the effective amounts herein.

14. Regarding applicants' remarks about pyrimidine compounds, it is noted that "During examination, claims are given their broadest reasonable interpretation. See *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)." Pyrimidine compounds," interpreted broadly, would read on all compounds having pyrimidine moiety, including those well-known antiviral compounds. Further, Administering any of the compounds having pyrimidine moiety would have reasonably been expected to increase the level metabolites of pyrimidine, such as uridine.

15. Subject matters as claimed to claim 34, and limited to those wherein *pyrimidine compound* is uridine, orotic acid and orotidine would be favorably considered. Note, claim 42 read on uridine *compounds*, i.e. any derivatives of uridine.